CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

APPROVAL LETTER

AADA 63-165/S-003, S-005, S-006

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

JUL 9 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug applications submitted pursuant to Section 314.70 of the Regulations dated March 28, 1991 (S-003 and S-006) and May 23, 1991 (S-005) regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP), 2 mg/mL.

Reference is also made to your amendments dated May 11, 1993.

The supplemental applications provide for:

S-003: additional dosage strengths of 75 mg/vial and 100 mg/vial.

S-005: alternate use of a continuous processing vial preparation, filling, capping and rinsing manufacturing line.

S-006: labeling for the new fill sizes.

We have completed the review of these supplemental applications, and they are approved. However, at the time of next printing revise your package insert as described below. Revised labeling may be submitted with an annual report provided you describe the changes.

A. INDICATIONS AND USAGE, first sentence, revise to read -

ADRIAMYCIN PFS® (Doxorubicin HCl Injection USP) has been used...

B. WARNINGS

1. paragraph 2, third sentence -

cumulative [spelling]

2. paragraph 4, third sentence -

...1000/mm^3... [add "/"]

3. paragraph 8, first sentence -

On intravenous administration of doxorubicin, extravasation...
[delete "HCl" and add comma]

C. REFERENCES

1. Revise reference #4 to read -

National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

2. Revise reference #7 to read -

American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990:47:1033-1049.

We remind you that you must comply with the requirements for an approved abbreviated antibiotic application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

7/8/93

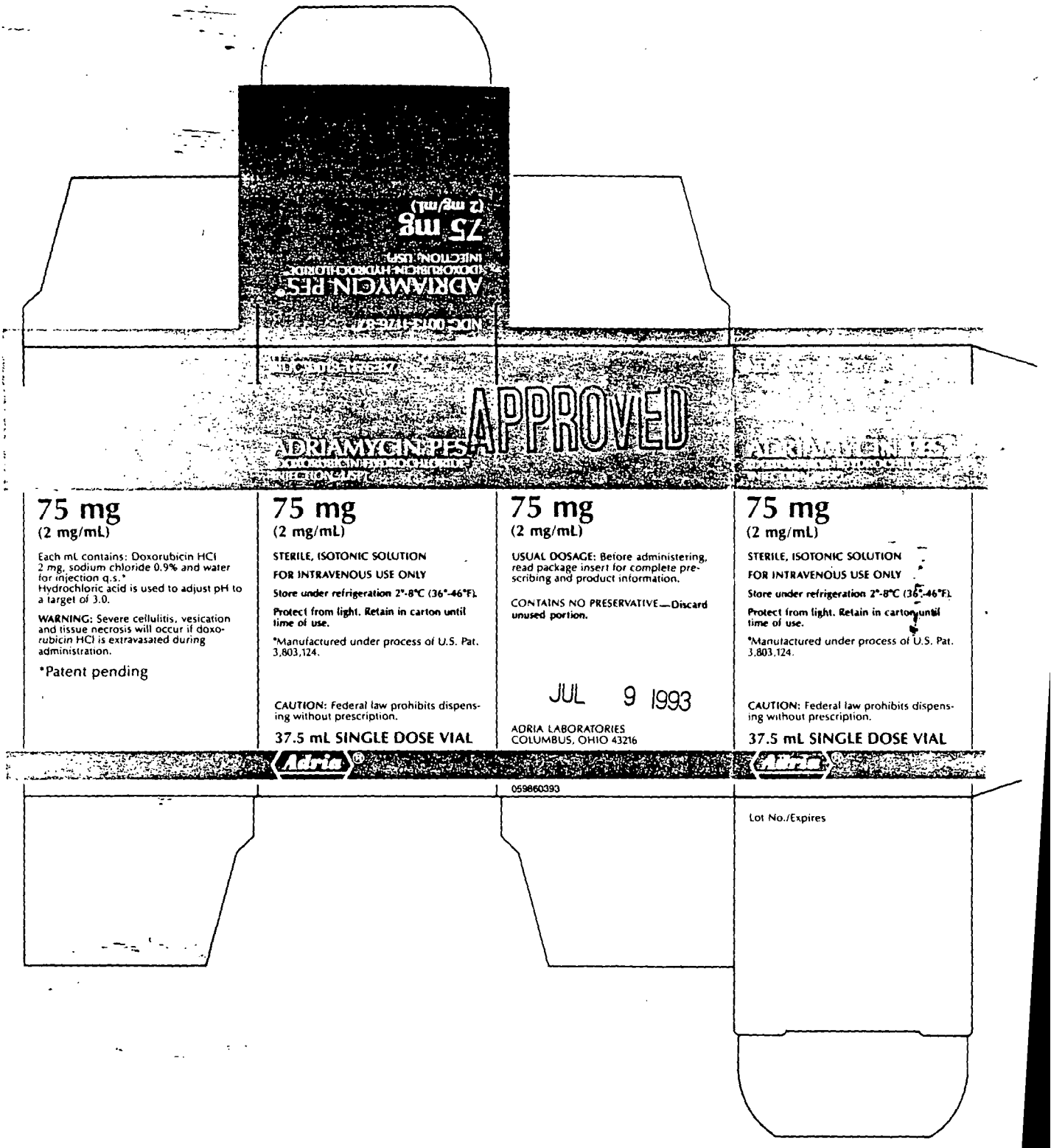
C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

APPROVED DRAFT LABELING


APPROVED
75 mg
(2 mg/mL)
Each mL contains: Doxorubicin HCl 2 mg, sodium chloride 0.9% and water for injection q.s.* Hydrochloric acid is used to adjust pH to a target of 3.0.
WARNING: Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin HCl is extravasated during administration.
*Patent pending
75 mg
(2 mg/mL)
STERILE, ISOTONIC SOLUTION
FOR INTRAVENOUS USE ONLY
Store under refrigeration 2°-8°C (36°-46°F).
Protect from light. Retain in carton until time of use.
*Manufactured under process of U.S. Pat. 3,803,124.
CAUTION: Federal law prohibits dispensing without prescription.
37.5 mL SINGLE DOSE VIAL
75 mg
(2 mg/mL)
USUAL DOSAGE: Before administering, read package insert for complete prescribing and product information.
CONTAINS NO PRESERVATIVE—Discard unused portion.
JUL 9 1993
ADRIA LABORATORIES
COLUMBUS, OHIO 43216
75 mg
(2 mg/mL)
STERILE, ISOTONIC SOLUTION
FOR INTRAVENOUS USE ONLY
Store under refrigeration 2°-8°C (36°-46°F).
Protect from light. Retain in carton until time of use.
*Manufactured under process of U.S. Pat. 3,803,124.
CAUTION: Federal law prohibits dispensing without prescription.
37.5 mL SINGLE DOSE VIAL
Adria
059860393
Lot No./Expires

ADRIAMYCIN PFS®
(DOXORUBICIN HCl INJECTION, USP)
AADA 63-165
100 mg Vial Label
Part # 059940393

Each mL contains: Doxorubicin HCl 2 mg, sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust pH to a target of 3.0.

Store under refrigeration, 2°-8°C (36°-46°F).

Protect from light. Retain in carton until time of use.

USUAL DOSAGE: Before administering, read package insert for complete prescribing and product information.

NDC 0013-1177-88

ADRIAMYCIN PFS®
(DOXORUBICIN HYDROCHLORIDE INJECTION, USP)

100 mg
(2 mg/mL)

STERILE, ISOTONIC SOLUTION FOR INTRAVENOUS USE ONLY

CAUTION: Federal law prohibits dispensing without prescription.

50 mL SINGLE DOSE VIAL

059940393

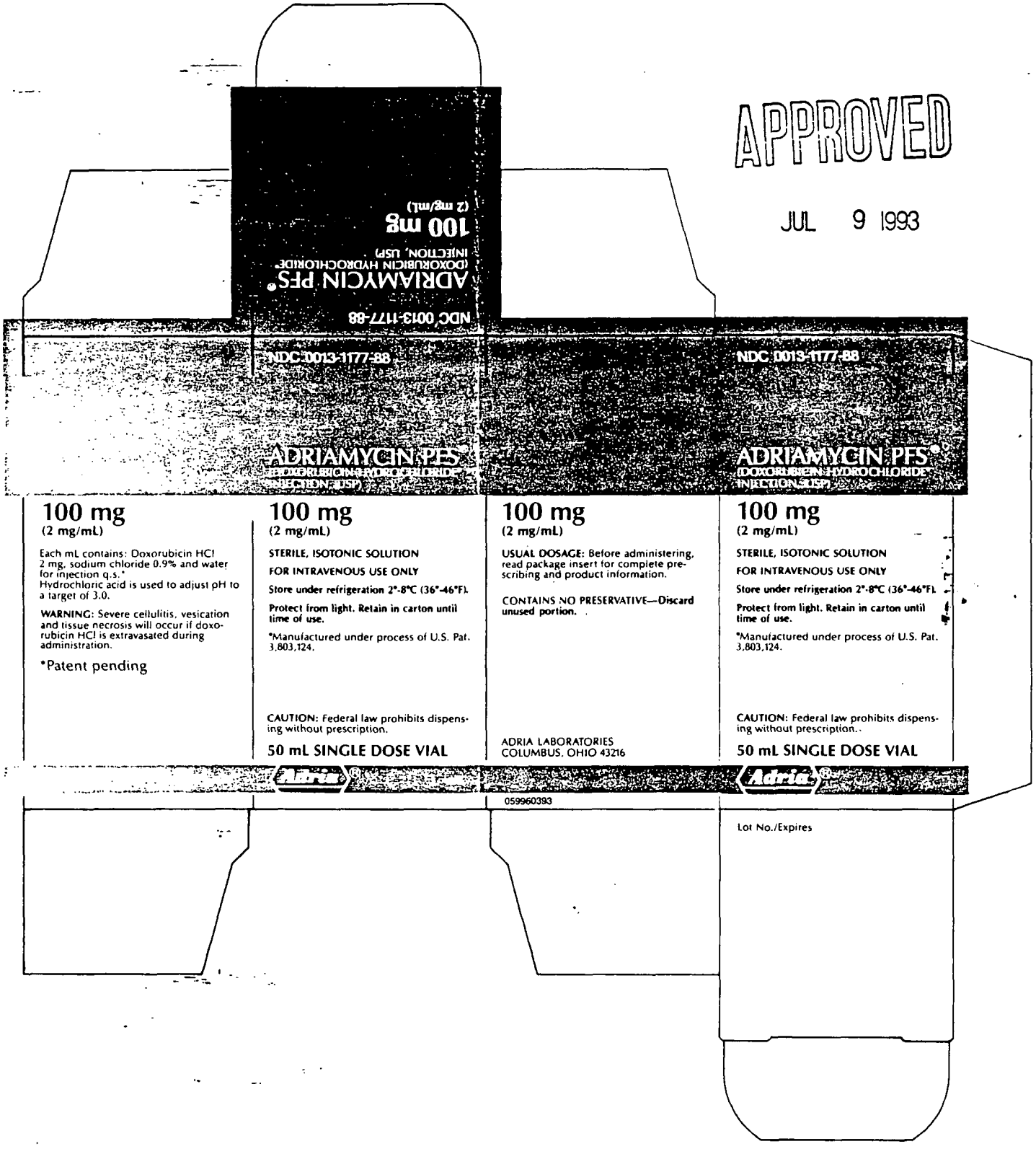
WARNING: Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin HCl is extravasated during administration.

CONTAINS NO PRESERVATIVE – Discard unused portion.

ADRIA LABORATORIES
COLUMBUS, OHIO 43216

Lot No.:
Exp.:

APPROVED
JUL 9 1993



APPROVED

JUL 9 1993

NDC 0013-1177-88

ADRIAMYCIN PFS®
(DOXORUBICIN HYDROCHLORIDE)
INJECTION, USP

100 mg
(2 mg/mL)

NDC 0013-1177-88

ADRIAMYCIN PFS®
(DOXORUBICIN HYDROCHLORIDE)
INJECTION, USP

100 mg
(2 mg/mL)

Each mL contains: Doxorubicin HCl 2 mg, sodium chloride 0.9% and water for injection q.s.* Hydrochloric acid is used to adjust pH to a target of 3.0.

WARNING: Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin HCl is extravasated during administration.

*Patent pending

100 mg
(2 mg/mL)

STERILE, ISOTONIC SOLUTION

FOR INTRAVENOUS USE ONLY

Store under refrigeration 2°-8°C (36°-46°F).

Protect from light. Retain in carton until time of use.

*Manufactured under process of U.S. Pat. 3,803,124.

CAUTION: Federal law prohibits dispensing without prescription.

50 mL SINGLE DOSE VIAL

Adria®

100 mg
(2 mg/mL)

USUAL DOSAGE: Before administering, read package insert for complete prescribing and product information.

CONTAINS NO PRESERVATIVE—Discard unused portion.

ADRIA LABORATORIES
COLUMBUS, OHIO 43216

059960393

NDC 0013-1177-88

ADRIAMYCIN PFS®
(DOXORUBICIN HYDROCHLORIDE)
INJECTION, USP

100 mg
(2 mg/mL)

STERILE, ISOTONIC SOLUTION

FOR INTRAVENOUS USE ONLY

Store under refrigeration 2°-8°C (36°-46°F).

Protect from light. Retain in carton until time of use.

*Manufactured under process of U.S. Pat. 3,803,124.

CAUTION: Federal law prohibits dispensing without prescription.

50 mL SINGLE DOSE VIAL

Adria®

Lot No./Expires

Adria®

ADRIAMYCIN PFS®

(DOXORUBICIN HYDROCHLORIDE INJECTION, USP)

FOR INTRAVENOUS USE ONLY

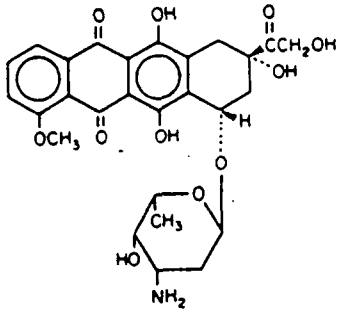
APPROVED
JUL 9 1993

059220393

WARNINGS

1. Severe local tissue necrosis will occur if there is extravasation during administration (See Dosage and Administration). ADRIAMYCIN PFS must not be given by the intramuscular or subcutaneous route.
2. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m². This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. ADRIAMYCIN PFS should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION: Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. The structural formula is as follows:



$C_{27}H_{29}NO_{11} \cdot HCl$
Formula Weight-579.99

.HCl

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.

ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP) is a sterile, isotonic solution containing no preservative, for intravenous use only, available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg), 37.5 mL (75 mg), and 50 mL (100 mg) single dose vials and 100 mL (200 mg) multidose vial.

Each mL contains doxorubicin hydrochloride and the following inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust pH to a target pH of 3.0.

CLINICAL PHARMACOLOGY: Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetic studies show the intravenous administration of normal or radiolabeled doxorubicin is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4 to 5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40 to 50% of the administered dose being recovered in the bile or the feces in seven days. Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Doxorubicin does not cross the blood brain barrier.

INDICATIONS AND USAGE: ADRIAMYCIN® (Doxorubicin HCl, USP) for injection has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, lymphomas of both Hodgkin and non-Hodgkin types, bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types and gastric carcinoma.

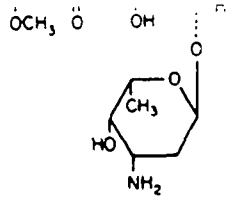
A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the central nervous system not to be significantly responsive to ADRIAMYCIN therapy.

CONTRAINDICATIONS: ADRIAMYCIN therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of ADRIAMYCIN induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended to start ADRIAMYCIN in such cases. ADRIAMYCIN treatment is contraindicated in patients who received previous treatment with complete cumulative doses of ADRIAMYCIN and/or daunorubicin.

WARNINGS: Special attention must be given to the cardiac toxicity exhibited by ADRIAMYCIN. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m². This limit appears to be lower (400 mg/m²) in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The total dose of ADRIAMYCIN administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of ADRIAMYCIN therapy. Children appear to be at particular risk for development of delayed doxorubicin cardiotoxicity in that doxorubicin impairs myocardial growth as they mature, leading to possible subsequent development of congestive heart failure during early adulthood.

Cardiac failure is often not favorably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. A baseline EKG and EKGs performed prior to each dose or course after 300 mg/m² cummulative dose has been given is suggested. Transient EKG changes consisting of T-wave flattening, S-T depression and arrhythmias lasting for up to two weeks after a dose or course of ADRIAMYCIN are presently not considered indications for suspension of ADRIAMYCIN therapy. ADRIAMYCIN cardiomyopathy has been reported to be associated with a persistent reduction in the voltage of the QRS wave, a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiography or radionuclide angiography. None of these tests have yet been confirmed to consistently identify those individual patients that are approaching their maximally tolerated cumulative dose of ADRIAMYCIN. If test results indicate change in cardiac function associated with ADRIAMYCIN the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after ADRIAMYCIN administration.



$C_{27}H_{29}NO_{11} \cdot HCl$
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Acute life-threatening arrhythmias have been reported to occur during or within a few hours after ADRIAMYCIN administration.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 to 14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as 1000mm³ are to be expected during treatment with appropriate doses of ADRIAMYCIN. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay ADRIAMYCIN therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

ADRIAMYCIN may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of ADRIAMYCIN.

Toxicity to recommended doses of ADRIAMYCIN is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin. (See Dosage and Administration).

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of ADRIAMYCIN given by i.v. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin HCl extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle (See Dosage and Administration). If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein.

ADRIAMYCIN and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Usage in Pregnancy—Safe use of ADRIAMYCIN in pregnancy has not been established. ADRIAMYCIN is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. Therefore, the benefits to the pregnant patient should be carefully weighed against the potential toxicity to fetus and embryo. The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated.

PRECAUTIONS: Initial treatment with ADRIAMYCIN requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

Like other cytotoxic drugs, ADRIAMYCIN may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

ADRIAMYCIN imparts a red coloration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

ADRIAMYCIN is not an anti-microbial agent.

ADVERSE REACTIONS: Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity (See Warnings). Other reactions reported are:

Cutaneous—Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in children, and onycholysis have been reported in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with ADRIAMYCIN administration.

Gastrointestinal—Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5 to 10 days after administration. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dosage regimen consisting of administration of ADRIAMYCIN on three successive days results in the greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe infections which can be fatal. This reaction has been reported in patients with acute non-lymphocytic leukemia treated with a 3-day course of ADRIAMYCIN combined with cytarabine. Anorexia and diarrhea have been occasionally reported.

Vascular—Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local—Severe cellulitis, vesication and tissue necrosis will occur if ADRIAMYCIN is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported (See Dosage and Administration).

Hypersensitivity—Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other—Conjunctivitis and lacrimation occur rarely.

OVERDOSAGE: Acute overdosage with ADRIAMYCIN enhances the toxic effects of mucositis, leukopenia and thrombopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis. **The 200 mg vial is packaged as a multiple dose vial and caution should be exercised to prevent inadvertent overdosage.**

Chronic overdosage with cumulative doses exceeding 550 mg/m² increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

DOSAGE AND ADMINISTRATION: Care in the administration of ADRIAMYCIN will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of ADRIAMYCIN, extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, local infiltration with an injectable corticosteroid and flooding the site with normal saline has been reported to lessen the local reaction. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. If ulceration begins, early wide excision of the involved area should be considered.[1]

The most commonly used dosage schedule is 60 to 75 mg/m² as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dosage schedule is weekly doses of 20 mg/m² which has been reported to produce a lower incidence of congestive heart failure. Thirty (30) mg/m² on each of three successive days repeated every 4 weeks has also been used. ADRIAMYCIN dosage must be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL—give ½ normal dose, > 3 mg/dL—give ¼ normal dose.

It is recommended that ADRIAMYCIN PFS be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Dextrose Injection USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADRIAMYCIN should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that ADRIAMYCIN PFS be mixed with other drugs.

ADRIAMYCIN has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

Handling and Disposal: Skin reactions associated with ADRIAMYCIN have been reported. Caution in the handling of the solution must be exercised and the use of gloves is recommended. If ADRIAMYCIN PFS contacts the skin or mucosae, immediately wash thoroughly with soap and water.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP)
Sterile, single use only, contains no preservative
NDC 0013-1136-91 10 mg vial, 2 mg/mL, 5 mL, 10 vial packs.
NDC 0013-1146-91 20 mg vial, 2 mg/mL, 10 mL, 10 vial packs.
NDC 0013-1156-79 50 mg vial, 2 mg/mL, 25 mL, single vial packs.
NDC 0013-1176-87 75 mg vial, 2 mg/mL, 37.5 mL, single vial packs.
NDC 0013-1177-88 100 mg vial, 2 mg/mL, 50 mL, single vial packs.

Store under refrigeration, 2°-8° C (36°-46° F). Protect from light and retain in carton until time of use. Discard unused solution.

Sterile, multidose vial, contains no preservative.
NDC 0013-1166-83 200 mg, 2 mg/mL, 100 mL multidose vial, single vial packs.

Store under refrigeration, 2°-8° C (36°-46°F). Protect from light and retain in carton until contents are used.

References

1. Rudolph R et al: Skin Ulcers Due to ADRIAMYCIN. Cancer 38:1087-1094, Sept. 1976.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, March 15, 1985.
4. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc. D., Director of Pharmacy Services. Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
5. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J. Australia 1:426-428, 1983.
6. Jones R. et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca—A Cancer Journal for Clinicians Sept/Oct, 258-263, 1983.
7. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic drugs in hospitals. Am J Hosp Pharm 47:1033-1049, 1990.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. AM J Hosp Pharm 1986; 43:1193-1204

extravasation have occurred. The injection [illegible]
If it is known or suspected that subcutaneous extravasation has occurred, local infiltration with an injectable corticosteroid and flooding the site with normal saline has been reported to lessen the local reaction. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. If ulceration begins, early wide excision of the involved area should be considered.[1]

The most commonly used dosage schedule is 60 to 75 mg/m² as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dosage schedule is weekly doses of 20 mg/m² which has been reported to produce a lower incidence of congestive heart failure. Thirty (30) mg/m² on each of three successive days repeated every 4 weeks has also been used. ADRIAMYCIN dosage must be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL—give ½ normal dose, > 3 mg/dL—give ¼ normal dose.

It is recommended that ADRIAMYCIN PFS be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Dextrose Injection USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADRIAMYCIN should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that ADRIAMYCIN PFS be mixed with other drugs.

ADRIAMYCIN has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

Handling and Disposal: Skin reactions associated with ADRIAMYCIN have been reported. Caution in the handling of the solution must be exercised and the use of gloves is recommended. If ADRIAMYCIN PFS contacts the skin or mucosae, immediately wash thoroughly with soap and water.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP)
Sterile, single use only, contains no preservative
NDC 0013-1136-91 10 mg vial, 2 mg/mL, 5 mL, 10 vial packs.
NDC 0013-1146-91 20 mg vial, 2 mg/mL, 10 mL, 10 vial packs.
NDC 0013-1156-79 50 mg vial, 2 mg/mL, 25 mL, single vial packs.
NDC 0013-1176-87 75 mg vial, 2 mg/mL, 37.5 mL, single vial packs.
NDC 0013-1177-88 100 mg vial, 2 mg/mL, 50 mL, single vial packs.

Store under refrigeration, 2°-8° C (36°-46° F). Protect from light and retain in carton until time of use. Discard unused solution.

Sterile, multidose vial, contains no preservative.
NDC 0013-1166-83 200 mg, 2 mg/mL, 100 mL multidose vial, single vial packs.

Store under refrigeration, 2°-8° C (36°-46°F). Protect from light and retain in carton until contents are used.

References

1. Rudolph R et al: Skin Ulcers Due to ADRIAMYCIN. Cancer 38:1087-1094, Sept. 1976.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, March 15, 1985.
4. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc. D., Director of Pharmacy Services. Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
5. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J. Australia 1:426-428, 1983.
6. Jones R. et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca—A Cancer Journal for Clinicians Sept/Oct, 258-263, 1983.
7. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic drugs in hospitals. Am J Hosp Pharm 47:1033-1049, 1990.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs, AM J Hosp Pharm 1986; 43:1193-1204.

ADRIA LABORATORIES
COLUMBUS, OHIO 43216

059220393 March 8, 1993

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

CHEMISTRY REVIEW(S)

AADA 63-165/S-003, S-005, S-006

NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental applications provide for:
S-003: for additional dosage strengths of 75 mg/vial and 100 mg/vial,
S-005: alternate use of a continuous processing vial preparation, filling, capping and rinsing manufacturing line,
S-006: labeling for the new fill sizes.

DATE(S) OF SUBMISSION(S)
March 28, 1991
May 23, 1991
May 11, 1993 (covered by this review)

PHARMACOLOGICAL CATEGORY
Antitumor Agent

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP (SVS)

POTENCY
2 mg/mL - 10, 20, 50, 75, 100, 200 mg/vial

RX OR OTC
℞

SAMPLES
N/A

RELATED IND/NDA/DMF
50-629
50-467
62-057
62-206

Page(s) 8

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Review

6/9/93

AADA 63-165/S-003

NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for additional dosage strengths 75 mg/vial and 100 mg/vial.

DATE(S) OF SUBMISSION(S)
March 28, 1991

PHARMACOLOGICAL CATEGORY
Antitumor Agent

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP

POTENCY
2 mg/mL - 10, 20, 50, (75, 100 - proposed), 200 mg/vial

RX OR OTC
℞

SAMPLES
N/A

RELATED IND/NDA/DMF
50-629
50-467
62-057

STERILIZATION
N/A

LABELING

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

Page(s) 1

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Chem Review

Components / controls

5/22/92

Deficiency
Drug Master File references with accompanying authorization should be provided for all packaging components. Also included should be a listing of the components with the corresponding vendor commodity numbers, and page references to the DMFs to permit access to technical information contained therein. Also include the specification documentation for each packaging component.

STABILITY
No batches were manufactured and no stability was generated.
Deficiency
Please provide stability data and batch records from one lot of each proposed fill size (15 - 20% of the maximum proposed batch size).

REMARKS AND CONCLUSION

RECALLS | Reviewer: Eric P. Duffy | Date Completed

ORDER OF REVIEW
The application submission covered by this review was taken in the date order of receipt YES

1/22/92

AADA 63-165/S-005

NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for alternate use of a continuous processing vial preparation, filling, capping and rinsing manufacturing line.

DATE(S) OF SUBMISSION(S)
May 23, 1991

PHARMACOLOGICAL CATEGORY
Antitumor Agent

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP

POTENCY
2 mg/mL - 10, 20, 50, 200 mg/vial

RX OR OTC
℞

SAMPLES
N/A

RELATED IND/NDA/DMF

STERILIZATION
N/A ← validation reqd.

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION

Page(s) 1

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Chem Rev.

5/22/92

Mfg and Composition

The following deficiency comments should be communicated to the firm:

The application fails to contain major portions of required information, and therefore has not been comprehensively reviewed. We offer the following comments at the present time, and will offer comprehensive comment when all required information has been submitted.

1. Please provide a completed batch record, and stability data from a batch produced by the proposed alternate manufacturing process.

2. Validation of the proposed filling process should be provided.

3. Please revise your exhibit Master Batch Record to incorporate the maximum batch size.

3. Please describe any revisions to in-process control procedures.

RECOMMENDATION: NOT APPROVABLE - MAJOR

RECALLS	Reviewer	Date Completed
	Eric P. Duffy	

ORDER OF REVIEW
The application submission covered by this review was taken in the date order of receipt YES

cc:

ED. Duffy for JDH
1/22/92

AADA 63-165/S-004
NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for optional use of the facilities at Albuquerque, New Mexico (Adria SP, or Columbus, Ohio (Adria Laboratories) for testing, packaging, and labeling.

DATE(S) OF SUBMISSION(S)
May 23, 1991

PHARMACOLOGICAL CATEGORY
Antitumor Agent

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP

POTENCY
2 mg/mL - 10, 20, 50, 200 mg/vial

RX OR OTC
℞

SAMPLES
N/A

RELATED IND/NDA/DMF

STERILIZATION

LABELING

BIOEQUIVALENCY STATUS

ESTABLISHMENT INSPECTION
EER - pending (requested 5/20/92)

COMPONENTS

COMPOSITION

MANUFACTURING

CONTROLS

PACKAGING

STABILITY

REMARKS AND CONCLUSION
The firm is in the process of transfering all responsibilities for this product from Columbus OH to the manufacturing site at Albuquerque NM. This supplement provided for optional QC testing, labeling, and packaging at the Albuquerque NM facility. EER for the operations at the new facility is required.

RECOMMENDATION: APPROVABLE pending satisfactory EER acceptable 5/22/92

RECALLS

Reviewer
Eric P. Duffy

Date Completed

ORDER OF REVIEW
The application submission covered by this review was taken in the date order of receipt YES

cc:

5/20/92

AADA 63-165/S-007

NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for a manufacturing rework procedure.

DATES OF SUBMISSIONS
November 3, 1992
April 29, 1993 - amendment

PHARMACOLOGICAL CATEGORY
Antitumor Antibiotic

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP

POTENCY
2 mg/mL - 10, 20, 50, 200 mg/vial

RX OR OTC
℞

SAMPLES
N/A

RELATED IND/NDA/DMF

STERILIZATION
N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS
Same as approved.

COMPOSITION
Same as approved

MANUFACTURING
The supplement proposes establishing a general rework procedure for the following situations:

lot failure due to -

CONTROLS
N/A

PACKAGING
N/A

STABILITY
Stability data for the reworked Lot # DXD021 are provided:

6 months at 2° - 8° C - acceptable
[this is the recommended storage temperature]
3 months at 24° - 28° C
[94.6 % l.c. @ 3 mos/initial 106.4 % l.c.]
3 months at 33° - 37° C [60.7 % l.c. @ 3 mos]

MICROBIOLOGY
See review by KHMuhvich dated 5/11/93.

Page(s) 3

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Chem Review

Mfg process/sterility

RECOMMENDATION: APPROVAL

The following comment should be directed to the firm in the letter of approval: Please submit microbiological monitoring results from personnel in the rework area for the first production rework lot of the subject drug product. Samples should include fingertips and sleeves of gowns.

ORDER OF REVIEW
The application covered by this review was taken in date receipt order for review:

YES X NO

RECALLS	Reviewer	Date Completed
	Eric P. Duffy	

Endorsements: — DOV 1/18/93
193

AADA 63-165/S-007

NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for a manufacturing rework procedure.

DATE(S) OF SUBMISSION(S)
November 3, 1992

PHARMACOLOGICAL CATEGORY
Antitumor Antibiotic

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP

POTENCY
2 mg/mL - 10, 20, 50, 200 mg/vial

RX OR OTC
Rx

SAMPLES
N/A

RELATED IND/NDA/DMF
50-629
50-467
62-057

STERILIZATION
N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION

COMPONENTS
Same as approved.

COMPOSITION
Same as approved

MANUFACTURING
The supplement proposes establishing a general rework procedure for the following situations:

lot failure due to -

Master batch records for the rework procedure are provided:

Instructions and records -

C

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev.
Mfg / deficiencies
3/29/93

8. With respect to this rework procedure being applicable to lots where , you have not specified which would qualify a lot for rework and provided data that indicate that product degradation does not occur. In the absence of these data, or a demonstration batch the proposed rework procedure is not considered appropriate for rework due to .

9. Please provide any stability data available to date.

RECOMMENDATION: NOT APPROVABLE - MINOR

RECALLS	Reviewer	Date Completed
	Eric P. Duffy	

cc:

Endorsements: EDuffy 3/29/93

AADA 63-165/S-008

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NAME AND ADDRESS OF APPLICANT:
Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for change in the manufacturing process which calls for addition of Doxorubicin Hydrochloride USP to water for more ready dissolution.

DATES OF SUBMISSIONS
July 27, 1993

PHARMACOLOGICAL CATEGORY
Antitumor Antibiotic

TRADE NAME
Adriamycin PFS™

NONPROPRIETARY NAME
Doxorubicin Hydrochloride Injection USP

DOSAGE FORM
SVP

POTENCY
2 mg/mL - 10, 20, 50, 200 mg/vial

RX OR OTC
℞

SAMPLES
N/A

RELATED IND/NDA/DMF
50-629
50-467
62-057

STERILIZATION
N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS
Same as approved.

COMPOSITION
Same as approved

MANUFACTURING

CONTROLS
N/A

PACKAGING
N/A

STABILITY
N/A

MICROBIOLOGY
N/A

REMARKS AND CONCLUSION
The revised process is acceptable.

RECOMMENDATION: APPROVAL

ORDER OF REVIEW
The application covered by this review was taken in date receipt order for review:

YES X NO

RECALLS	Reviewer	Date Completed
	Eric P. Duffy	

Endorsements:

7/93

FYI by mw/10/7/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

MICROBIOLOGY REVIEW

CONSULTATIVE REVIEW TO HFD-600
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
October 22, 1992

ANDA/Supplement Number: AADA 63-165 / S-005

Document Date: June 11, 1991

Name and Address of Applicant:
Adria Laboratories
Division of Erbamount, Inc.
P.O.Box 16529
Columbus, Ohio 43216-6529

Name of Drug: Adriamycin PFS® (doxorubicin hydrochloride injection, USP)

Supplement Provides For: Post-approval submission of fill validation information for the batch process (approved January 30, 1991; validation information for the process is also submitted in this same 6-11-91 submission. This fulfills the commitment contained in the applicant's January 11, 1990 (sic, applicant's letter) submission.

Pharmacological Category: cytotoxic anthracycline antibiotic

Dosage Form: Sterile solution in single-use vials (2 mg/mL) with rubber stopper and aluminum seal:

5 mL (10 mg) fill in 6 mL vial,
10 mL (20 mg) fill in 10 mL vial,
25 mL (50 mg) fill in 30 mL vial, and
100 mL (200 mg) fill in 100 mL vial (multidose).

Conclusions and Recommendations: Recommend approval of supplement for sterility assurance. See **Review Notes** below.

Signature: Carol K Vincent 10-22-92
Carol K. Vincent, HFD-160

JMK 10/23/92

MA 10/23/92

Page(s) 10

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Micro Rev.
10/22/92

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #2

11 May 1993

A. 1. AADA: 63-165/S-007

APPLICANT: Adria Laboratories
P.O. Box 16529
Columbus, Ohio 43216-6529

2. PRODUCT NAMES: Doxorubicin Hydrochloride Injection USP
Adriamycin PFS™

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: SVP preservative-free solution for intravenous administration. **Single-dose vials:** 10 mg/5 mL in a 6 mL vial, 20 mg/10 mL in a 10 mL vial, 50 mg/25 mL in a 30 mL vial. **Multiple-dose vial:** 200 mg/100 mL in a 120 mL vial.

4. METHOD(S) OF STERILIZATION:
by

5. PRINCIPLE INDICATIONS: To produce regression of disseminated neoplastic diseases such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilm's tumor, neuroblastoma, sarcomas, breast & ovarian carcinoma, transitional bladder cell carcinoma, and various lymphomas.

6. PHARMACOLOGICAL CATEGORY: Antineoplastic antibiotic

B. 1. DATE OF INITIAL SUBMISSION: 3 November 1992

2. DATE OF AMENDMENT: **29 April 1993** Minor Amendment in response to the Agency's deficiency letter of 30 March 1993 **Subject of this review**

3. RELATED DOCUMENTS: **NDA's 50-629 & 50-467** held by the applicant for manufacture of Adriamycin PFS™ and Adriamycin RDF™, respectively
DMF's held by
Italy for production of the raw drug substance
DMF held by The for closures

4. ASSIGNED FOR REVIEW: 10 May 1993

C. REMARKS: Three questions concerning the sterility assurance of the manufacturing rework procedure for the subject drug product (Doxorubicin Hydrochloride Injection USP) were communicated to the applicant via letter. The applicant's response to all three questions was adequate.

D. CONCLUSIONS: The submissions are therefore recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

Kenneth H. Muhvich 5/11/93

Kenneth H. Muhvich, Ph.D.

cc:

1

DH Wolf 5/12/93

Page(s) 2

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Micro Rev. 2

5/12/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING

Amendment to Supplement

FPL

DATE OF REVIEW: May 26, 1993

ANDA #: 63-165/S-006

NAME OF FIRM: Adria

NAME OF DRUG: Trade: Adriamycin PFS®

Generic: Doxorubicin Hydrochloride Injection USP, 75 mg and 100 mg single dose vials.

DATE OF SUBMISSION: May 11, 1993

COMMENTS:

Container - For 75 mg and 100 mg: Satisfactory in FPL.

Carton - For 75 mg and 100 mg: Satisfactory in FPL.

Insert: Satisfactory in FPL.

However, at the time of next printing revise your package insert as described below. Revised labeling may be submitted with an annual report provided you describe the changes.

A. INDICATIONS AND USAGE, first sentence, revise to read -

ADRIAMYCIN PFS® (Doxorubicin HCl Injection USP) has been used...

B. WARNINGS

1. paragraph 2, third sentence -

cumulative [spelling]

2. paragraph 4, third sentence -

...1000/mm^3... [add "/"]

3. paragraph 8, first sentence -

On intravenous administration of doxorubicin, extravasation...
[delete "HCl" and add comma]

C. REFERENCES

1. Revise reference #4 to read -

   National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

2. Revise reference #7 to read -

   American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990:47:1033-1049.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. For the Record

   a. In a 5/15/92 conversation, Dr Williams (HFD-150) confirmed the 75 mg vial was acceptable.

   b. The last sentence in the first paragraph of the WARNINGS section was found to be acceptable in a 6/22/92 NA letter to the firm. The wording was confirmed by Ellen Cutler (HFD-150) in a 5/27/93 memo.

John Grace

6/1/93
6/1/93

//

REVIEW OF PROFESSIONAL LABELING

Supplement

DRAFT - FPL

DATE OF REVIEW: 5/14/92

AADA #: 63-165/S-00~~5~~ S-006

NAME OF FIRM: Adria

NAME OF DRUG: Trade:

Generic: Adriamycin PFS® (Doxorubicin Hydrochloride Injection USP) 75 mg and 100 mg single dose vials

DATE OF SUBMISSION: 3/28/91

COMMENTS:

Container: Satisfactory in draft for 75 mg and 100 mg, however we prefer "STERILE ISOTONIC SOLUTION" (rather than just "STERILE")

Carton: Satisfactory in draft for 75 mg and 100 mg

Insert: Not Satisfactory

A. Title

Relocate "USP" to appear at the end of the established name: Doxorubicin Hydrochloride Injection USP.

B. DESCRIPTION

1. paragraph 1, second sentence, revise to read:

Doxorubicin consists of a napthacenequinone...

2. paragraph 3, add:

37.5 mL (75 mg) and 50 mL (100 mg) single dose

3. The requirements of 21 CFR 201.57(a)(1)(ii) and (iv) must be met. We believe the route should be more specific than "parenteral".

C. CLINICAL PHARMACOLOGY, paragraph 2

We prefer (to rather than hyphen)

40% to 50%
4% to 5%

D. WARNINGS

1. paragraph 1, fourth sentence, revise to read:

...into account previous or... (delete "a")

2. paragraph 4, first sentence - we prefer:

...10 to 14 days...

E. PRECAUTIONS, paragraph 3 - we prefer:

...1 to 2 days...

F. ADVERSE REACTIONS, Gastrointestinal, first and second sentences revise to read:

...5 to 10 days..

The dosage regimen consisting...

G. DOSAGE AND ADMINISTRATION

1. Paragraph 2

a) first sentence - revise to read:

The most commonly used dosage schedule is 60 to 75 mg/m^2...

b) third sentence - revise to read:

An alternative dosage schedule is...

c) fourth sentence - revise to read:

Thirty (30) mg/m^2...

d) final sentence - we prefer:

... 1.2 to 3.0 mg/dL...

2. paragraph 4 - revise to read:

...with heparin or fluorouracil... (delete 5)

3. Add as paragraph 3:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

H. HOW SUPPLIED

1. single dose vials, storage statement, revise to read:

2°-8°C (36°-46°F). Protect from light...

2. single dose vials.

Move "Discard" statement to the next line.

3. multiple dose vials, storage statement, revise to read:

2°-8°C (36°-48°F). Protect from light and retain in carton until contents are used.

I. REFERENCES

Update reference #7 to read:

...Am J Hosp. Pharm. 1990; 47:1033-1049.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels, and carton and insert labeling, then prepare and submit final printed labels and labeling.

John Kenan 5/19/92

Div. of slogg
See record of phone conversation
5/19/92

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 25, 1992

FROM: Mark Anderson, CSO, Branch 5

SUBJECT: AADA 63-165/S-003 and S-005

TO: The record

John Harrison, Eric Duffy, Ph.D. and I spoke with Fred Grab in follow-up to the 9/21/92 conversation I had with Mr. Grab. After discussion, it was clarified that in order to gain approval of S-003 and S-005 Adria will need to prepare a test batch of at least 10% of the proposed maximum batch size which may be split filled into 75 mg and 100 mg vials. Ninety day accelerated stability data gathered prior to submission of the amendments to S-003 and S-005 will also be required.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 21, 1992

FROM: Mark Anderson, CSO

SUBJECT: AADA 63-165/S-003 and S-005 Requests by Adria to reconsider our 5/27/92 NA letters

TO: The record

I called Fred Grab, Adria Labs [(614) 764-8128] about his pending requests dated July 20, 1992 for meetings to discuss the not approvable letters Adria received for S-003 (which provides for additional dosage strengths of 75 and 100 mg/vial of Adriamycin PFS) and S-005 (which provides for use of a continuous processing vial preparation, filling, capping and exterior vial rinsing line to replace the manual line now in use). The Adria letters take exception to our reasons for not approving the supplements and request the above mentioned meetings if we do not agree with their proposals.

I told Mr. Grab that after internal discussion, we did not feel a meeting(s) would serve a useful purpose. However it was suggested that we instead have a conference call with Mr. Harrison, Dr. Duffy and Adria to clarify our position.

Mr. Grab said Adria is still especially concerned with the need to submit stability data and batch records for the 75 mg and 100 mg strengths prior to approval due to the expense of the raw materials and the possibility the products may expire prior to approval. He referred to discussions which he said were held between Mr. Harrison (and possibly others) and Mr. Warren Myers of Adria in November 1988 which was prior to submission of Adria's AADA 63-165 in January of 1989. It was and is Adria's understanding from that meeting that agreement was reached to permit intermediate fill sizes to be manufactured based on stability data generated on the largest and smallest fill sizes.

After checking, I told Mr. Grab I was unable to locate any November 1988 meeting minutes but that even if agreement was reached at that time that our policies are subject to change and that, as Dr. Duffy had previously explained (refer to 9/2/92 T. Con.), manufacture of one batch of each strength is necessary prior to approval. This is a policy we apply to all applicants.

Mr. Grab then asked if it would be possible to review other aspects of the supplements and resolve deficiencies such that they could be found approvable except for submission of stability data and batch records for the 75 and 100 mg fill sizes as a means of minimizing the possibility of product expiring before approval. I said I would relay this request to Mr. Harrison.

REVIEW OF PROFESSIONAL LABELING

Amendment to Supplement

NO LABELING SUBMITTED

DATE OF REVIEW: August 6, 1992

AADA #: 63-165/S-006 (New Correspondence)

NAME OF FIRM: Adira

NAME OF DRUG: Trade: Adriamycin PFS
Generic: Doxorubicin Hydrochloride Injection, USP

DATE OF SUBMISSION: July 20, 1992

COMMENTS:

We acknowledge the firm's commitment to submit final printed labeling as soon as the Division of Oncology/Pulmonary Drug Products approves the two NDA's associated with this product.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

J.Grace

FINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	[redacted]
☒ Original ☐ Follow-Up ☐ FUR	5/24/93	295-8360	

REQUESTOR'S NAME	DIVISION	MAIL CODE
Eric Duffy/Jena Weber	OGD	HFD- 635

APPLICATION AND SUPPLEMENT NUMBER
63-165/S-005

BRAND NAME	ESTABLISHED NAME
Adriamycin PFS	Doxorubicin HCl Injectinn, USP

DOSAGE AND STRENGTH	STERILE
10, 20, 50, 200 mg/vial	☒ YES ☐ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
SVS	

APPLICANT'S NAME
Adria Laboratories

ADDRESS
7001 Post Road
Dublin, OH

COMMENTS

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. Adria SP, Inc. 2272 Balloon Park Rd. Alburquerque, NM 87109	Manufacturing, Testing		[redacted]	
2. Continuous process full line Room 274			[redacted]	
3.			[redacted]	
4.			[redacted]	
5.			[redacted]	

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 5/15/92

NDA NUMBER: 63-165

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☐ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Adriamycin PFS

FIRM NAME: Adria

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr Williams - FDA Oncology Medical Officer for this drug; Ellen Cutler - CSO for Oncology Drugs

TELEPHONE NO.: 443-5197

I spoke with Dr Williams about the acceptability of a 75 mg single dose vial. He indicated it is ok:

1) reasonable as single dose
2) already have 50mg & 100mg

I spoke with Ellen Cutler about the 3/27/91 submission to NDA's 50-467 & 50-629. These submissions provide for combined inserts & we can't approve the supplements we have until they approve theirs. Ellen said still not received. I confirmed that she had received a copy of the review we sent over.

SIGNATURE: Yana Mille

DIVISION: Office of Generic Drugs

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service — 2-96c

Memorandum

te May 20, 1992

From Division of Generic Drugs — HFD- 632

Requestor's Name Eric Duffy/Dave Doleski — Phone 295-8360

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product X — Non Sterile Product _____

Application and Supplement No. 63-165/S-004

Brand Name *(if any)* ADRIAMYCIN PFS

Establishment Name, Dosage Form and Strength Doxorubicin Hydrochloride Injection USP

_____ Profile Class Code: SVP

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Adria Laboratories

Address: 7001 Post Rd., Dublin, OH 43017

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*) — **For HFD 320 Use** Status & Date of Inspection:

1. ADRIA Adria SP 4272 Balloon Park Rd. Alburquerque, NM — AC- 2/21/92
   ~~QC testing, labeling packaging~~
2. ASTA Adria SP 3700 Osuna Drive Suite 715 Albuquerque, NM — AC- 2/21/92
   QC testing, labeling, packaging
3. _____
4. _____
5. _____

Other Information or Special Requests: _____

****

For HFD-320 Use Only: Date Received: 5/21/92

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: _____ Date Completed: 5/22/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90) — ★U.S.GPO:1991-0-281-805/41633

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 12, 1992

FROM: Mark Anderson, CSO, Branch 5

SUBJECT: AADA 63-165/S-007 for Doxorubicin HCl Inj. by Adria
Request for Expedited Review

TO: The Record

I called Mr. Fred Grab, Regulatory Affairs at Adria [6140 764-8128] and informed him that his request for expedited review for the supplement dated November 3, 1992 has been denied. I explained that economic hardship, other than that caused by events outside the applicant's control, was not a grounds for granting expedited review.

Mr. Grab thanked me for the information and, although not in agreement, said he was not surprised as to our decision. He asked for an estimate as to how long it might be before the supplement was reviewed. I said, based on current workloads, it appeared the supplement would be reviewed within about 4 months - though I offered no assurance of this.

The conversation ended cordially.

11/12/92 called firm re relay decision See memo M. Anderson

OFFICE OF GENERIC DRUGS

EXPEDITED REVIEW REQUESTED

ANDA/AADA SUPPLEMENT #: 63-185 SC-007 APPLICANT: Adria Laboratories

DRUG: Doxorubicin HCl Injecton

DATE OF SUBMISSION: 11/3/92

The Office of Generic Drugs Policy and Procedure Guide #18-90 as revised on January 22, 1992 lists the following criteria for granting expedited review status to a supplemental new drug application. At least one of the criteria must be met.

1. **PUBLIC HEALTH NEED.** Events that affect the availability of a drug for which there is no alternative.

2. **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**

   a. Catastrophic events such as explosion, fire, storm damage.

   b. Events that could not have been reasonably foreseen, and for which the applicant could not plan. Examples include:

      ▲ abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and

      ▲ relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a.).

3. **AGENCY NEED.**

   a. Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.

   b. Federal or state legal/regulatory actions, including mandated formulation changes or labeling changes if it is in the Agency's best interest.

   c. Expiration-date extension or packaging change when the drug product is the subject of a government contract award.

RECOMMENDATIONS:

Branch CSO/Chemist	Grant/Deny	Mark Anderson 11/9/92 Signatures & Dates
Supervisory Chemist	Grant/Deny	E. Duffy 11/10/92 Signature & Date
Division Director	Grant/Deny	C. Greg Fry 11/10/92 Signature & Date

Although it is an extraordinary hardship, it doesn't meet a #6 of the policy.

COMMENTS: While there may be economic hardships involved our Policy + Procedure Guide # 18-90 does not "fit" this type of situation and applicant has not claimed a public health need.

CC: ANDA/S#, Division File, Doc. Room log, R.Pollock, CSO.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

CORRESPONDENCE

Adria
ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

May 11, 1993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

5c-005/AC
NDA SUPPLEMENT

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: **AADA 63-165/S-005**
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Amendment to Supplement

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.60 of Title 21 of the Code of Federal Regulations, we are submitting an amendment to the referenced application.

The purpose of this material is to respond to the Agency's deficiency letter of May 27, 1992.

As agreed during our telephone conversation of September 28, 1992 with Mr. Harrison, Mr. Duffy and Mr. Anderson, we have prepared one bulk solution and filled it on our process line into 75 and 100 mg vials. It was agreed that the information on the 75 and 100 mg vials would be sufficient to qualify all six vial sizes, 10, 20, 50, 75, 100 and 200 mg for manufacture on the process line. The batch records for these lots have been included in the amendment filed to /S-003, /S-006 to the titled AADA (also being submitted today), and are referenced in this amendment. Similarly, the requested accelerated stability data generated through 3 months has been included in the amendment to /S-003, /S-006 and referenced in this amendment.

The requested filling process validation documentation was incorporated in the validation package submitted to the Agency June 11, 1991. We have been informed by the Agency that the package has been found to be acceptable.

ORIGINAL

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

F L Grab

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: M. Anderson - CSO Branch V
E. Duffy - Reviewing Chemist Branch V

FLG/ps
Enclosures

Containers & carton
PI satisfactory
for approval per
(ADRIAMYCIN @ app 5/3/89)
[illegible] 5/20/93

Adria
ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

May 11, 1993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

SC-003/AM
SL-006/AM

NDA SUPPL AMENDMENT

RECEIVED

MAY 14 1993

GENERIC DRUGS

FPL

for Rev.
See SC-005 date 5-11-93 → 5-14-93 in vol 5.1

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: **AADA 63-165/S-003, /S-006**
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Amendment to Supplement

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.60 of Title 21 of the Code of Federal Regulations, we are submitting an amendment to the referenced application.

The purpose of this material is to respond to the Agency's deficiency letter of May 27, 1992.

As agreed during our telephone conversation of September 28, 1992 with Mr. Harrison, Mr. Duffy and Mr. Anderson, we have prepared one bulk solution and filled it on our continuous process line into 75 and 100 mg vials. The batch records have been included in the amendment filed to /S-003, /S-006 to the titled AADA and referenced in the amendment to /S-005, which is also being submitted today. Similarly, the requested accelerated stability data generated through 3 months has been included in the amendment to /S-003, /S-006 and referenced in the amendment to /S-005.

As requested, our labeling pieces have been revised. Enclosed are twelve final printed copies of all of our labeling pieces effected.

ORIGINAL

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: M. Anderson - CSO Branch V
E. Duffy - Reviewing Chemist Branch V

FLG/ps
Enclosures

Note: NAI Mark Anderson 10/15/92

Adria®

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, OH 43216-6529

October 6, 1992

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RECEIVED
OCT 0 9 1992
GENERIC DRUGS

Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
Division of Generic Drugs
ATTENTION: DOCUMENT CONTROL ROOM 150
HFD 600
5600 Fishers Lane
Rockville, MD 20857

to SC-003
NEW CORRESP SL-006
SC-005

RE: AADA 63-165/S-003, /S-005 & /S-006
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)

Dear Sir/Madame:

This letter is being submitted to the supplements to the titled application to document what we believe was agreed to during our conference phone conversation of September 25, 1992 with Mr. Harrison, Mr. Duffy and Mr. Anderson.

We had submitted a supplement March 28, 1991, assigned supplement numbers /S-003 and /S-006, to add two interim sizes, a 75 and 100 mg vial to the four sizes already approved. We also submitted a second supplement May 23, 1991, assigned supplement number /S-005, to qualify an automated line. FDA deficiency letters to both submissions requested a batch record and stability data.

It was agreed that accelerated stability data through 3 months generated on 75 and 100 mg vials prepared on the automated line would be satisfactory to support both supplements.

We would appreciate your confirming the correctness of our interpretation by signing and dating below.

John D. Harrison — 10/14/92
John Harrison (Branch Chief) — Date

E Duffy — 10/14/92
Eric Duffy (Chemistry Reviewer) — Date

ORIGINAL

We thank you for your assistance in this matter.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs
Generic Drugs

Desk Copy: Mark Anderson (Room 250 - Metro Park North II)

FLG/pss

ORIG

Adria®

ADRIA LABORATORIES

Mod labeling submitted
Prior will submit
when NFO-150 approves
labeling for NDAs.
Jessica 8/6/92

ADMINISTRATIVE OFFICES:

ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

AIRBORNE

July 20, 1992

RECEIVED

JUL 2 3 1992

GENERIC DRUGS

Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

S-003
S-006

ATTN: Michael G. Beatrice
Director, Chemistry II

Dear Mr. Beatrice:

Please refer to your letter dated May 27, 1992 regarding supplements S-003 and S-006 to AADA 63-165. These supplements provide for additional dosage strengths of 75 mg/vial and 100 mg/vial of Adriamycin PFS as well draft labeling for the new strengths.

The May 27, 1992 letter cites a number of deficiencies in the supplements and states they are not approvable. The deficiencies listed suggest that the supplements may not have contained sufficiently detailed explanations of the changes. The purpose of this letter is to provide that detail and to request that the supplements be reconsidered in light of this information.

The May 27, 1992 letter discusses the requirement for Drug Master File references for packaging components in general and specifically specification documentation and dimensional drawings for the proposed stoppers.

The supplement includes an Introduction Section that may have been overlooked that states the supplement specifies certain changes in the application and all other information in AADA 63-165 remains the same. The original application contains information about the container - closure system on pages 03-253 to 03-283. This information includes a reference to the glass (p.03-265), a DMF reference to the stopper (p.03-267), and diagrams of the stoppers (p.03-266). These remain the same for the 75 mg and 100 mg strengths. Components for these strengths are listed on pages 004 and 005 of the supplement. The additional sizes of the vials for these strengths are described on pages 014 to 017 of the supplement. Although the vial sizes changed, the vial neck size and the stoppers remain the same as described in AADA 63-165.

The May 27,1992 letter requests the submission of stability data and batch records from one lot of each proposed fill size (15%-20% of the maximum propose batch size).

AADA 63-165 for Adriamycin PFS manufactured at Adria-SP was approved on January 30, 1991. The original application provided for strengths of 10 mg, 20 mg, 50 mg, and 200 mg/vial. All four strengths were approved based upon stability for one lot of 10 mg and one lot of 200 mg only. Supplements S-003 and S-006 were submitted on March 28, 1991.

Supplements S-003 an S-006 also included by reference the batch records in the original AADA with the the addition of the specific pages in these records revised by the addition of the 75 mg/vial and 100 mg/vial strengths, pages 010 and 011 of the supplement.

The information submitted in supplement S-003 was based upon the experience with the original AADA that only the smallest and largest sizes must be placed on stability and on discussion with Division staff. Since the bulk drug substance, the formulation, the method of manufacture of the finished dosage form, and the concentration are identical for all strengths, it was reasonable to conclude that the two strengths provided for in the supplement would be encompassed by the stability data in the original application in the same manner as were the 20 mg and 50 mg strengths. In addition, please note that the supplement included a commitment to place commercial batches on stability and to recall any lots not meeting specifications. We are, therefore, dismayed to learn that new requirements are apparently being applied by the Division. Considerable time, effort and expense would be required to comply with this new requirement and would result in substantial delay in the approval of the supplement.

Adria respectfully requests that the Division rescind the request for new stability data on the 75 and 100 mg strengths included in Supplements S003 on the basis that stability of the 10 mg and 200 mg product has already been established.

2 (in A)

The May 17, 1992 letter requests the submission of revised final printed labeling.

Adria markets Adriamycin under two NDAs (50-629 and 50-467) and two AADAs (63-165 and 62-057). We have been working with the Division of Oncology/Pulmonary Drug Products to consolidate the inserts under these applications into one combined insert for all applications in order to maximize the uniformity and to avoid the potential for using the wrong insert in the various products. This activity is underway and a revised draft will be forwarded to the Division shortly. Please see the attached letter from the Office of Generic Drugs indicating that Adria should revise inserts in accord with the Divisions comments and submit final printed labeling to the two AADAs when that activity is complete and approval has been received from the Division. Therefore, in order to avoid the possibility of different inserts for the same product, please consider awaiting the approval of the revised insert before changing the insert for AADA 63-165.

Adria believes the information provided in this letter is sufficient to provide for the reevaluation of the supplements and requests that they be approved. In the event that the Agency differs with our conclusions, we request a meeting to discuss the matter. I will call the week of August 3, 1992 to review this letter and our request.

Sincerely,

for

Angel Luis Canales
Director of Regulatory Affairs
Marketed Drugs and QC/QA

cc: Dr. R. Jerussi

Adria®
ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

AIRBORNE

July 20 1992

NEW CORRESP
SC-005

RECEIVED
JUL 2 3 1992
GENERIC DRUGS

Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ATTN: Michael G. Beatrice
Director, Chemistry II

Dear Mr. Beatrice:

Please refer to your letter dated May 27, 1992 regarding supplement S-005 of AADA 63-165. This supplement provided for alternate use of a continuous processing vial preparation, filling, capping and exterior vial rinsing line.

The referenced letter cites a number of deficiencies and, additionally indicates major portions of the supplement are missing. This letter suggests that the supplement may not have adequately explained the nature of the changes Adria is proposing. In addition, information submitted with respect to the manufacture may not have been properly brought to the attention of the reviewer. The purpose of this communication is to identify the areas of possible misunderstanding and to request a reevaluation of supplement S-005.

The process for the manufacture of Adriamycin PFS at Adria-SP by the process is the same as the process approved in the original AADA on January 30, 1991. The only change requested in S-005 is to replace several manual operations with automatic operations. The net result is decreased handling of the product and the reduction of the number of people required in the sterile room. The process more closely approximates the manufacture of Adriamycin at Farmitalia Carlo Erba, an affiliate of Adria, who produced the product for the US market prior to the approval of AADA 63-165. The use of the word verses "batch" in describing the change may have been a poor choice of words. Adriamycin is manufactured in batches by both methods. The supplement provides for the automation of a number of steps that are currently than being done manually. The attached schematic serves to compare the two operations and to identify the differences in a clearer manner.

A complete process validation package consisting of three volumes of information was submitted as a supplement on June 11, 1991. This timing was in accordance with an agreement with the FDA by letter dated 12/22/89 and agreed upon by Adria on 1/4/90. The agreement stipulated that the process validation should be submitted by six months after approval of the application. Approval was on January 30, 1991.

The submission includes validation information for both the batch and continuous process. We were unable to reference the validation package in supplement S-005 since its submission predated the June 11, 1991 supplement.

The letter of May 27,1992 requests revision of the Master Batch Record to incorporate the maximum batch size. Please see page 027 of the supplement for the statement of the batch size. It is stated as ____ Please note that this is not the maximum scale up of the batch in the original application, but represents the capacity of the largest compounding equipment currently avaialble at Adria-SP.

In response to a question in the May 27, 1992 letter, there were no revisions in the in-process controls.

Adria believes that the supplement S-005 is complete and reviewable as it stands. We therefore request that the review of this supplement proceed based upon the clarification provided in this letter. We apologize for any misunderstanding that may have occurred regarding the nature of the change and the data and information provided.

In the event that the Office disagrees with our conclusions and request, we would appreciate an opportunity to meet to discuss the matter. I will call the week of August 3, 1992 to discuss this letter and our request.

Sincerely

Angel Luis Canales
Director of Regulatory Affairs
Marketed Drugs and QC/QA

cc: Dr. R. Jerussi

AADA 63-165/S-005

MAY 27 1992

Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

Dear Sir:

Reference is made to your supplemental antibiotic drug application submitted pursuant to Section 314.70 of the Regulations dated May 23, 1991, regarding your abbreviated antibiotic drug application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for alternate use of a continuous processing vial preparation, filling, capping and rinsing manufacturing line.

The supplemental application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

The application fails to contain major portions of required information, and therefore has not been comprehensively reviewed. We offer the following comments at the present time, and will offer comprehensive comment when all required information has been submitted.

1. Please provide a completed batch record, and stability data from a batch produced by the proposed alternate manufacturing process.

2. Validation documentation for the proposed aseptic filling process should be provided.

3. Please revise your exhibit Master Batch Record to incorporate the maximum batch size.

4. Please describe any revisions to in-process control procedures.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a major amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/27/92

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

Draft for JDH
5/22/92

NOTED: JHannay 6/3/91

SE-005

Adria

ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

May 23, 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: AADA 63-165
Adriamycin PFS (Doxorubicin HCl Injection, USP)

Gentlemen:

In accordance with the provisions of Paragraph 314.70 of Title 21 of the Code of Federal Regulations, we are presenting a supplement to the referenced application.

The purpose of this supplement is to provide for a cess as an alternative to the currently approved process for the manufacture of Adriamycin PFS. The supplement includes a comparison of the and processes to demonstrate their comparability. The batch records have been reformatted to become specific and to incorporate previous forms into the batch records. The formulation and manufacturing procedure are the same as approved in the application.

Very truly yours,

Warren L. Myers
Director, Regulatory Affairs
Marketed Products/Generic Drugs

WLM:df

RECEIVED
MAY 29 19

MAILING ADDRESS: PO Box 16529 Columbus OH 43216-6529

ORIGINAL

GENERIC DRUGS

SC-003

ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:

ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

March 28, 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA NO. 63-165 REF. NO. SC-003
NDA SUPPL FOR Pediatric Use

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Contains 3 carton
subfactory
PI - need revision
5/20/92

NDA NO 63-165 REF. NO. SC-006
NDA SUPPL FOR Controlled Rev

Re: AADA 63-165
Adriamycin PFS® (doxorubicin hydrochloride USP)
Injection

Dear Sir:

In accordance with the provisions of Paragraph 314.70(b) of Title 21 of the Code of Federal Regulations, we are submitting a supplement to the referenced application.

The purpose of the supplement is to provide for two additional vial sizes, 75mg and 100mg. These additional sizes are within the range covered by the approved application (10mg to 200mg).

Please note that the draft labeling reflects currently approved labeling. A separate supplement has been submitted containing the revisions requested by the Office of Generic Drugs. These changes, when approved, will be made for the sizes included in this supplement.

Very truly yours,

Warren L. Myers
Director, Regulatory Affairs
Marketed Products/Generic Drugs

WLM:df

RECEIVED
APR 2 1991
GENERIC DRUGS

MAILING ADDRESS: P.O. Box 16529, Columbus OH 43216-6529

ORIGINAL

AADA 63-165/S-004

JUN - 1 1992

Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

Dear Sir:

Reference is made to your supplemental antibiotic drug application submitted pursuant to Section 314.70 of the Regulations dated April 2, 1991, regarding your abbreviated antibiotic drug application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for optional use of the facilities at Albuquerque, New Mexico (Adria SP), or Columbus, Ohio (Adria Laboratories) for testing, packaging, and labeling of the product.

We have completed the review of this supplemental application and it is approved. Our letter of January 30, 1991 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/ 5/31/92

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Adria
ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
7001 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

SC-0084

April 2, 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: AADA 63-165
Adriamycin PFS™ (Doxorubicin HCI Injection, USP)

Gentlemen:

In accordance with the provisions of Paragraph 314.70 of Title 21 of the Code of Federal Regulations, we are presenting a supplement to the referenced application.

The purpose of this supplement is to provide for the option of conducting certain testing and packaging/labeling operations either at our facility at Albuquerque, New Mexico (Adria-SP) or in Columbus, Ohio (Adria Laboratories). The tests and procedures would not differ from those described in the approved application.

Very truly yours,

Warren L. Myers
Director, Regulatory Affairs
Marketed Products/Generic Drugs

WLM:df

RECEIVED
APR 5

MAILING ADDRESS: P.O. Box 16529 Columbus OH 43216-6529

ORIGINAL

GENERIC DRUGS

AADA 63-165/S-003/S-006

MAY 27 1992

Adria Laboratories
Attn: Warren L. Meyers
P.O. Box 16529
Columbus, OH 43216-6529

Dear Sir:

Reference is made to your supplemental antibiotic drug applications submitted pursuant to Section 314.70 of the Regulations dated March 28, 1991, regarding your abbreviated antibiotic drug application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP), 2 mg/mL.

The supplemental applications provide for additional dosage strengths of 75 mg/vial and 100 mg/vial (S-003) and draft labeling for the new fill sizes (S-006).

The supplemental applications are deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. Drug Master File references with accompanying authorization should be provided for all packaging components. Also included should be a listing of the components with the corresponding vendor commodity numbers and page references to the DMFs to permit access to technical information contained therein. The specification documentation should also be included for each packaging component. Dimensional drawings should be provided for the proposed stoppers as well as information on composition.

2. Please provide stability data and batch records from one lot of each proposed fill size (15 - 20% of the maximum proposed batch size).

3. Please revise and submit twelve final printed copies of your insert labeling based upon the following comments:

   Container: Satisfactory in draft for 75 mg and 100 mg, however we prefer "STERILE ISOTONIC SOLUTION" (rather than just "STERILE")

   Carton: Satisfactory in draft for 75 mg and 100 mg

Insert: Not Satisfactory

A. Title

Relocate "USP" to appear at the end of the established name: Doxorubicin Hydrochloride Injection USP.

B. DESCRIPTION

1. paragraph 1, second sentence, revise to read:

Doxorubicin consists of a napthacenequinone...

2. paragraph 3, add:

37.5 mL (75 mg) and 50 mL (100 mg) single dose

3. The requirements of 21 CFR 201.57(a)(1)(ii) and (iv) must be met. We believe the route should be more specific than "parenteral".

C. CLINICAL PHARMACOLOGY, paragraph 2

We prefer (to rather than hyphen)

40% to 50%
4% to 5%

D. WARNINGS

1. paragraph 1, fourth sentence, revise to read:

...into account previous or... (delete "a")

2. paragraph 4, first sentence - we prefer:

...10 to 14 days...

E. PRECAUTIONS, paragraph 3 - we prefer:

...1 to 2 days...

F. ADVERSE REACTIONS, Gastrointestinal, first and second sentences revise to read:

...5 to 10 days..

The dosage regimen consisting...

G. DOSAGE AND ADMINISTRATION

1. Paragraph 2

a) first sentence - revise to read:

The most commonly used dosage schedule is 60 to 75 mg/m^2...

b) third sentence - revise to read:

An alternative dosage schedule is...

c) fourth sentence - revise to read:

Thirty (30) mg/m^2...

d) final sentence - we prefer:

... 1.2 to 3.0 mg/dL...

2. paragraph 4 - revise to read:

...with heparin or fluorouracil... (delete 5)

3. Add as paragraph 3:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

H. HOW SUPPLIED

1. single dose vials, storage statement, revise to read:

2°-8°C (36°-46°F). Protect from light...

2. single dose vials.

Move "Discard" statement to the next line.

3. multiple dose vials, storage statement, revise to read:

2°-8°C (36°-48°F). Protect from light and retain in carton until contents are used.

I. REFERENCES

Update reference #7 to read:

...Am J Hosp. Pharm. 1990; 47:1033-1049.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a minor amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 12/6/02

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

SUPPLEMENT NOT APPROVABLE

AADA 63-165/S-007

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

MAY 19 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug application dated November 3, 1992, submitted pursuant to 21 CFR 314.70 of the Regulations, regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

Reference is also made to your amendment dated April 29, 1993.

The supplemental application provides for a manufacturing rework procedure.

We have completed the review of this supplemental application and it is approved.

Please note and acknowledge the following request:

> Please submit microbiological monitoring results from personnel in the rework area for the first production rework lot of the subject drug product. Samples should include fingertips and sleeves of gowns.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/

5/19/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

April 29, 1993

AIRBORNE

SC-007 \ Am
NDA SUPPL AMENDMENT

RECEIVED

APR 3 0 1993

GENERIC DRUGS

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: **AADA 63-165/S-007**
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Minor Amendment to Supplement

MINOR AMENDMENT

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.60 of Title 21 of the Code of Federal Regulations, we are submitting a minor amendment to the referenced application.

The purpose of this material is to respond to the Agency's deficiency letter of March 30, 1993.

In response to various questions, a revised Master Batch Record (MBR) is included herein.

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

F L Grab

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: M. Anderson - CSO Branch V
E. Duffy - Reviewing Chemist Branch V

FLG/pss
Enclosures

ORIGINAL

AADA 63-165/S-007

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

MAR 30 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug application dated November 3, 1992, submitted pursuant to 21 CFR 314.70 of the Regulations, regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for a manufacturing rework procedure.

The supplemental application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. The sterile operating area should be specified (i.e., class 100, sterile core # X, etc.). For filling, the approved filling line for this product should be specified.

2. The environmental microbial monitoring of the designated rework area should be described, in particular as it relates to personnel. Provide data from such monitoring.

3. Use of should be specified as is required for the approved manufacturing process.

4. Adjustment of for subpotent rework lots should not be provided for unless a means for ontent determination is established.

5. Time limits for production should be established per 21 CFR 211.111. In particular, for lots proposed for rework due to sterility assurance failure and pH limits being exceeded, where the stability of the product has not been determined, the proposed limits should be suitably short. Time limits for bulk solution holding prior to fill should also be established.

6. Bioburden limits for the compounded bulk solution should be established.

7. Filled vial accountability limits should be established.

8. With respect to this rework procedure being applicable to lots where there you have not specified which would qualify a lot for rework and provided data that indicate that product degradation does not occur. In the absence of these data, or a demonstration batch the proposed rework procedure is not considered appropriate for rework due to

9. Please provide any stability data available to date.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 3/29/93

C.Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Note: request denied
Request denied
review in turn 11/12/92
Mark Anderson

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont Inc

P O. Box 16529
Columbus. OH 43216-6529

November 3, 1992

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
Division of Generic Drugs
ATTENTION: DOCUMENT CONTROL ROOM 150
HFD 600
5600 Fishers Lane
Rockville, MD 20857

NDA NO. _____ REF. NO. 3C-002

NDA SUPPL FOR Manufacturing Chan
3C-002 AR

RE: AADA 63-165
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
SUPPLEMENT

SUPPLEMENT - EXPEDITED REVIEW REQUESTED

Dear Sir/Madame:

In accordance with the provisions of Paragraph 314.70 of Title 21 of the Code of Federal Regulations, we are submitting a supplement to the referenced application.

The purpose of this supplement is to qualify a rework procedure. The supplement includes certificates of analysis for a batch which was subsequently reworked. The certificates demonstrate their comparability.

The formulation, packaging materials, specifications and analytical methods for the reworked material are identical to those approved in the AADA. Other than for those activities involved in the rework, the manufacturing process is also unchanged.

We are requesting an expedited review because the batch that was reworked was a full commercial batch of an expensive material. We would appreciate a prompt review and approval so that the majority of the reworked batch can be placed into commerce at a time sufficiently before its expiration date of September 1993. Our not being able to do so would impose an extraordinary hardship on us. We would be willing to do whatever is needed to assist in expediting the review and approval of this supplement.

Should any clarification be desired, please feel free to contact me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs
Generic Drugs

FLG/ps

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

June 23, 1993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

to SC-007
NEW CORRESP

RE: AADA 63-165/S-007
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP)
Acknowledgement Letter

Dear Sir/Madame:

We are submitting this document in response to an Agency request in their letter of May 19, 1993 approving the titled supplement.

We have noted and acknowledge the following:

> "Please submit microbiological monitoring results from personnel in the rework area for the first production rework lot of the subject drug product. Samples should include fingertips and sleeves of gowns."

At the time our approved rework procedure is next carried out, it is our intention to perform the microbiological monitoring requested by the FDA. The results of such monitoring will then be submitted to the Agency.

Should any clarification be desired, please call me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

RECEIVED
JUN 25 1993
GENERIC DRUGS

FLG/pss

AADA 63-165/S-008

Adria Laboratories
Attn: Frederick L. Grab, Ph.D.
P.O. Box 16529
Columbus, OH 43216-6529

OCT 12 1993

Dear Sir:

This is in reference to your supplemental antibiotic drug application dated July 27, 1993, submitted pursuant to 21 CFR 314.70, regarding your abbreviated antibiotic application for Adriamycin PFS™ (Doxorubicin Hydrochloride Injection USP).

The supplemental application provides for a change in the manufacturing process which calls for addition of Doxorubicin Hydrochloride USP to water for more ready dissolution.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated antibiotic application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 10/8/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Noted:
To Mr. Harrison
Mark Anderson
7/30/93

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont, Inc.

P.O. Box 16529
Columbus, Ohio 43216-6529

July 27, 1993

AIRBORNE

NDA NO. _____ REF NO. SCI-008
NDA SUPPL FOR Manufacturing Rev.

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED
JUL 28 1993
GENERIC DRUGS

RE: AADA 63-165
ADRIAMYCIN PFS® (Doxorubicin Hydrochloride Injection, USP) 2 mg/mL

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

cK J. Harrison 7/30/93

Dear Sir/Madame:

In accordance with the provisions of 314.70(c)(1) of Title 21 of the Code of Federal Regulations, we are submitting a Special Supplement - Changes Being Effected to the referenced application.

The purpose of this submission is to reverse the order of two steps involved in the compounding of the initial, concentrated solution. Attached is a copy of the revised page (5B) from our Master Batch Record where Steps C and D have been reversed. The currently

[illegible] of the vessel during the [illegible]

Since the change in the order of addition should not have a negative affect on the product, we are implementing this change August 9.

Should any clarification be desired, please call me at (614)764-8128.

Very truly yours,

Frederick L. Grab, Ph.D.
Director, Regulatory Affairs,
Generic Drugs

Desk Copy: Mark Anderson

FLG/pss